REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 21, 23, 35, 36, 38, and 39 are pending and under active consideration in this application.

b. Priority

On pages 2 and 3 of the Office Action, the Examiner denies this application the benefit of the priority date of U.S. Provisional Patent Application No. 60/441,241 (the "Priority Application").[1] The Examiner asserts that the Priority Application cover sheet clearly indicates that not all CDs shown on the cover sheet were received by the Office, and that there is no record of SEQ ID NOs: 128, 131, 133, 477, 480, and 482 in the file of the Priority Application.

Applicant submits herewith Figures 142, 145, and 147, which disclose instant SEQ ID NOs: 128 and 477, 131 and 480, and 133 and 482. *See* Appendix B. These figures and the Priority Application sequence listing were contained on separate CDs filed with the Priority Application. The Priority Application coversheet submitted with the office action reply of April 21, 2008 (the "Previous Reply") indicates only one missing CD. Accordingly, the Office must have at least received either the CD containing the above-mentioned figures or the CD containing the sequence listing with the Priority Application. Applicant submits that the Examiner has provided no evidence that the CDs received by the Office with the Priority Application do not disclose the instantly claimed sequences. Applicant respectfully requests that the Examiner review these CDs and confirm that they indeed do not disclose the instantly claimed sequences, whether in the figures or the sequence listing, or both. In view of the foregoing, Applicant submits that the instantly claimed subject matter has written description support in the Priority Application as required under 35 U.S.C. § 112, first paragraph. Accordingly, the priority date of the instant claims is the filing date of the Priority Application, which is January 17, 2003.

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[1] The Examiner also refers to U.S. Prov. App. No. 60/363,124 in the Office Action. Applicant believes that the Examiner intended to refer to the Priority Application. Applicant requests clarification if this belief is erroneous.

2. Patentability Remarks

a. 35 U.S.C. § 101

On pages 3-8 of the Office Action, the Examiner rejects claims 21, 23, 35, and 36 under 35 U.S.C. § 101, because the claimed subject matter allegedly lacks a specific, substantial, or credible utility or a well established utility. Specifically, the Examiner alleges that SEQ ID NOs: 477 (VGAM 142), SEQ ID NO: 480 (VGAM 145), and SEQ ID NO: 482 (VGAM 147) do not have utility because none of them has been shown to actually bind and regulate specific target transcripts of INHBA, ZNF36[2], and ACADSB, respectively, and are therefore are no more than speculative.

Applicant submits herewith experimental evidence that the SEQ ID NOS: 477, 480, and 482 are capable of inhibiting the expression of the asserted host target transcripts of INHBA, ZNF36 and ACADSB, respectively. Quantitative reverse transcription PCR was performed to demonstrate inhibition of host target transcripts INHBA, ZNF36, and ACADSB by infecting HeLa cells comprising these target transcripts with Vaccinia virus comprising the viral miRNAs set forth in SEQ ID NOS: 480, 482, and 477. As shown in Appendix A, the uninfected HeLa cells had 3.8-, 3.2-, and 49.3-fold higher levels of INHBA, ZNF36 and ACADSB transcripts, respectively, compared to infected cells. Accordingly, one of skill would conclude that the miRNAs encoded by [V]GAM145, [V]GAM147, and [V]GAM142 (SEQ ID NOs: 480, 482, and 477, respectively), reduce expression of the asserted targets INHBA, ZNF36, and ACADSB mRNAs, respectively. In view of the foregoing, the claimed nucleic acids have specific, substantial, and credible utility as regulators of INHBA, ZNF36, and ACADS. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 101.

b. 35 U.S.C. § 112, first paragraph

(1) Alleged lack of utility

On page 8 of the Office Action, the Examiner rejects claims 21, 23, 35, and 36 under 35 U.S.C. § 112, first paragraph because the claimed subject matter allegedly lacks utility. Applicant disagrees in view of the foregoing evidence that the claimed nucleic acids are supported by a specific, substantial, and credible utility. Applicant respectfully requests that the

[2] ZNF36 is also referred to in the art as ZKSCAN1.

Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

(2) Alleged new matter

On page of the Office Action, the Examiner rejects claims 38 and 39 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the probes of the rejected claims are new matter because there is no written description of the claimed probe comprising SEQ ID NO: 128, 131, 133, 477, 480, or 482 wherein these sequences are viral genes in the application as originally filed, and there is not adequate support that the inventor at the time of filing contemplated making a probe for the sequences, wherein each sequence is a viral gene. Applicant respectfully disagrees.

With regard to whether the sequences are viral genes, paragraphs 1942, 1984, and 2012 of the specification as filed, respectively, disclose that each of VGAM142, VGAM145, and VGAM147, "is a **viral gene** contained in the genome of Vaccinia virus" (emphasis added). As to which SEQ ID NOs are related to these VGAMs, Table 1, lines 892-896, 913-917, and 927-931, respectively, disclose that: [V]GAM142 is related to SEQ ID NOs: 128 and 477; [V]GAM145 is related to SEQ ID NOs: 131 and 480; and, [V]GAM147 is related to SEQ ID NOs: 133 and 482. Further, the specification at paragraph 0011 discloses that, "the invention provides several substantially pure nucleic acids ... each encoding a novel **viral gene of the VGAM group** ... [and] **probes comprising the nucleic acids**" (emphasis added). Accordingly, Applicant submits that the application as filed clearly provides support for the claimed probes comprising SEQ ID NO: 128, 131, 133, 477, 480, or 482, wherein these sequences are viral genes. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 38 and 39 under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC

Dated: August 29, 2008

On behalf of: Teddy C. Scott, Jr., Ph.D.
Registration No. 53,573

By: /Ron Galant, Ph.D./
Ron Galant, Ph.D.
Registration No. 60,558
Customer No. 37808

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC
180 N. Stetson Ave., Suite 4525
Chicago, IL 60601
312.819.1900 (main)
312.602.3955 (E-fax)
312.873.3613 (direct)

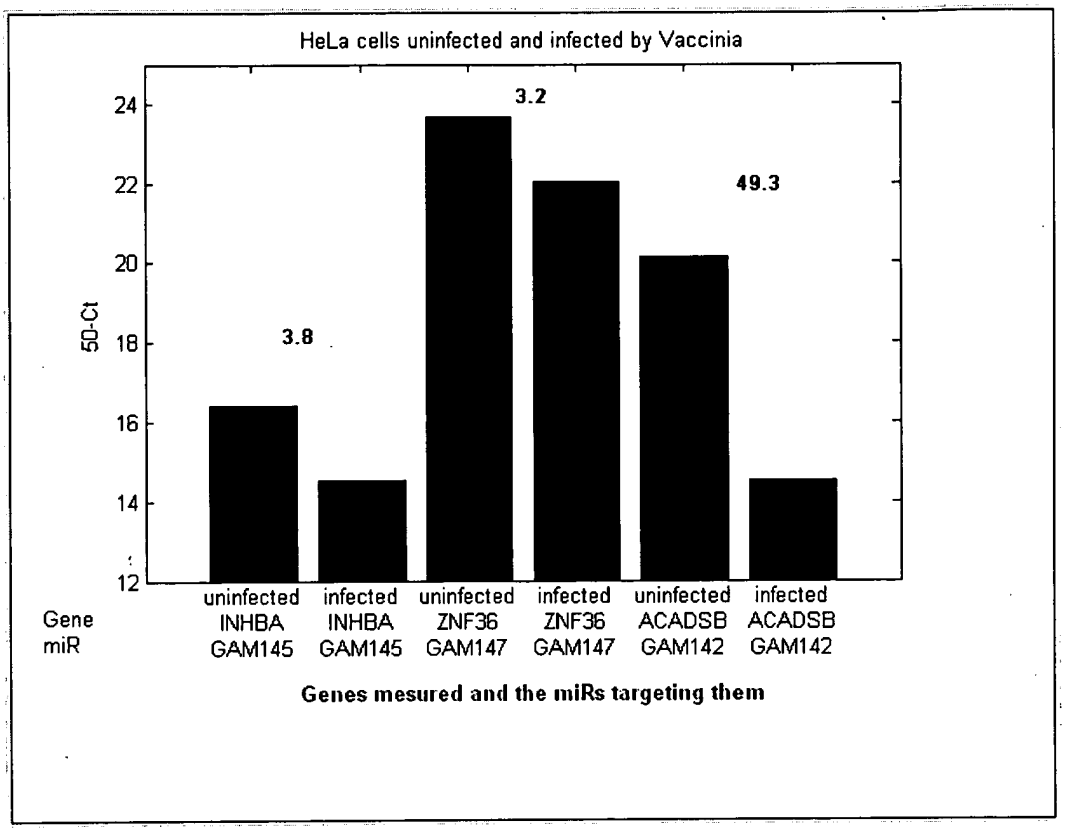
APPENDIX A

In order to validate INHBA (SEQ ID NO: 904), ZNF36 (SEQ ID NO: 3627) and ACADSB (SEQ ID NO: 838) as targets of the Vaccinia virus miRNAs GAM145(SEQ ID NO: 480), GAM147(SEQ ID NO: 482) and GAM142((SEQ ID NO: 477) respectively, Applicant infected HeLa cells, which do not express Vaccinia miRNAs, with Vaccinia virus. After infection, RNA was isolated, and the mRNA levels of INHBA, ZNF36 and ACADSB were quantified using specific primers by the SYBR RT-qPCR method (see below).

Measuring the amount of initial mRNA was based on the observation that the amount of cDNA generated from the mRNA doubles with every cycle of PCR. Therefore, after N cycles, there is 2^N times as much. In order to quantify the initial amount of mRNA, the cycle number at which the increase in fluorescence (and thus the amount of cDNA) was exponential, was measured. A threshold at this level of fluorescence was set. This threshold is indicated as the cycle threshold, or Ct. To compare the differences in quantity between a specific mRNA in two different samples, the Ct was calculated in each of the samples, and the delta Ct (dCt) was calculated. The fold-change between the amount of mRNA in the two samples was represented by 2^{dCt}. In order to make the measurements of mRNA levels intuitive, 50-Ct values were calculated from Ct values and charted, such that lower 50-Ct values indicate lower levels of mRNA.

The expression of the targets INHBA, ZNF36 and ACADSB in infected and non infected HeLa cells is presented in Figure 1.

Figure 1



Expression levels of INHBA, ZNF36 and ACADSB in cells infected with Vaccinia virus and expressing Vaccinia miRNAs were 3.8-, 3.2- and 49.3-fold lower (as measured by 50-Ct), respectively, than in non infected cells which did not express Vaccinia virus miRNAs.

Figure 1 clearly shows that infection with Vaccinia virus which expressed GAM145, GAM147 AND GAM142 caused a significant decrease in the levels of INHBA, ZNF36 and ACADSB mRNAs respectively, thereby indicating that these miRNAs regulate the expression of their respective target transcripts.

Viral miRs Target Validation

Samples

HeLa Cells were infected with Vaccinia virus. RNA extracted from infected and non-infected control cells was used for quantification of Vaccinia virus miRNA target mRNAs (INHBA, ZNF36 and ACADSB) by quantitative RT-PCR. The RNA of virally infected cells and of non-infected cells was used for mRNA quantification by RT-PCR.

Sample (RNA)	miR	Targets		
HeLa cells - control				
HeLa cells infected with Vaccinia	Vaccinia	INHBA	ZNF36	ACADSB

Reverse Transcription

1μg of total RNA was reverse-transcribed using Superscript II.

Quantification by RT-qPCR

mRNA was quantified by the real-time-qPCR SYBR Green method, using 7500 Fast Real time PCR system, AB applied Bio-systems. Each mRNA was tested using 2 primer pairs, and was done in triplicates. Ct values were normalized to TBP and RPS20 as house keeping genes.

The following primers were used for mRNA quantification:

Primer_id	sequence	Gene name
16328-Fwd	AGAAGAGACCCGATGTCACC	INHBA
16329-Rev	CCTTGGAAATCTCGAAGTGC	INHBA
16330-Rev	CTGACAGGTCACTGCCTTCC	INHBA
16331-Fwd	GGTGAAGATCGAGGACATGG	ZNF36
16332-Rev	CAGCCTTTGAGGTTGACTCC	ZNF36
16333-Fwd	ATTATGGGAGCGCATTTCC	ZNF36
16334-Rev	TCTCCTCAGGGTTTTTCTGC	ZNF36
16335-Fwd	CCATGAAATACACGCTGTGC	ACADSB
16336-Rev	ACTCCTCCTCAATCCAGTCC	ACADSB
16337-Fwd	CAGAAGGAGGTGTGCATCC	ACADSB
16338-Rev	GCTTGAGCTGCTTGATCTCC	ACADSB

	Primers for Target	
House keeping Gene	Fwd	Rev
TBP	TATAATCCCAAGCGGTTTGC	CACAGCTCCCCACCATATTC
RPS20	TATAATCCCAAGCGGTTTGC	CACAGCTCCCCACCATATTC

Data Analysis

Normalization was done by subtracting the Ct value of the geometric mean of two house keeping gene TBP and RPS20. Ct values were determined using a default threshold of 0.2 in the 7500 Fast Real time PCR system, by ABI.

APPENDIX B

FIG. 142A

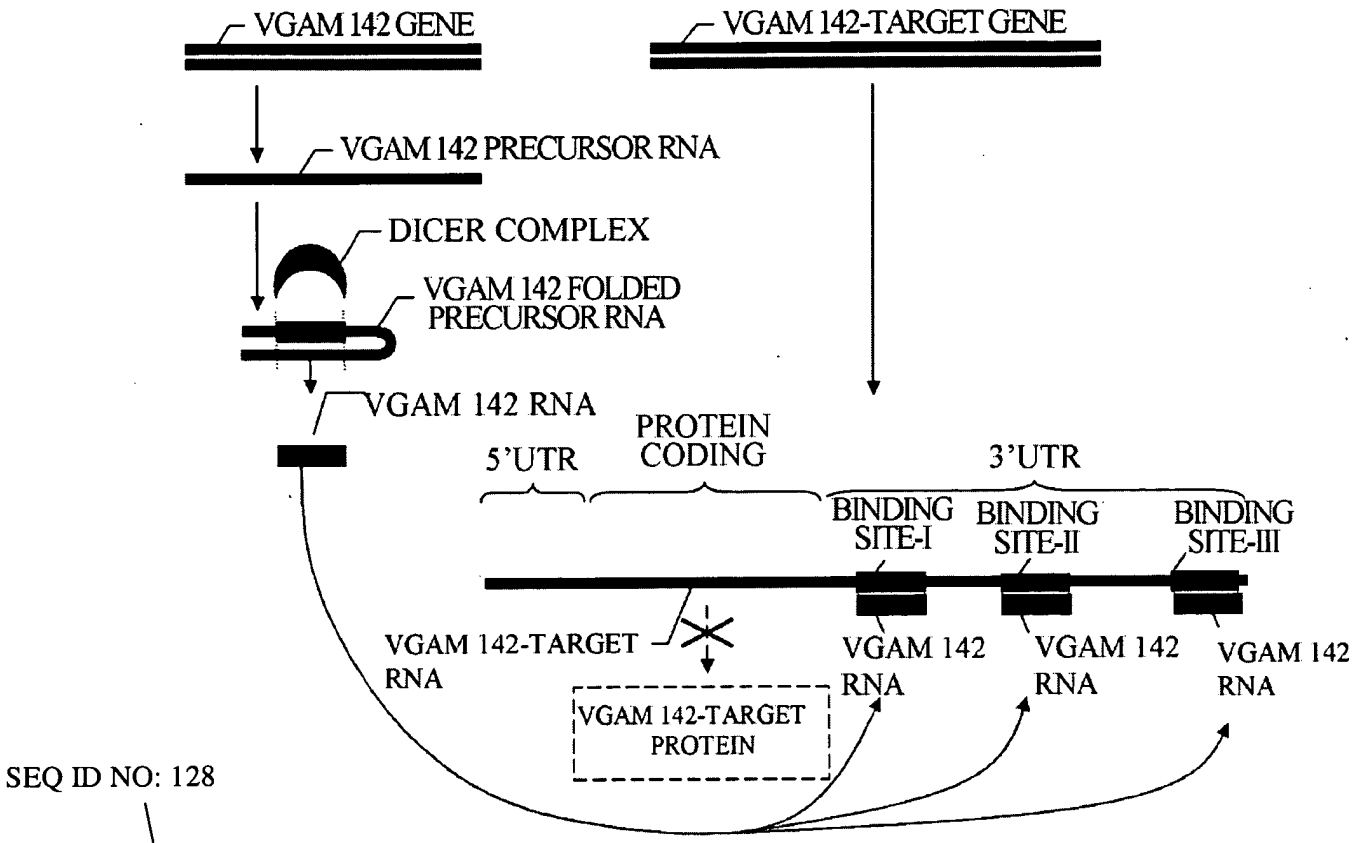


FIG. 142B

SEQ ID NO: 128

CACCGCCTCTAGATATCGCCTTTATTTCCACATTAGATGG **SEQ ID:40001**
TAAATCCAATAGTGAAACTATCTTTTTAGGAATGTATGG
ACTCGCGTTTAGAGGAGTG

CGCCTTTATTTCCACATTAGATGG **SEQ ID:40002**

SEQ ID NO: 477

FIG. 142C

```
   CG          ATCG--  TTTAT    ACATT        AAATCCA
CAC  CCTCTAGAT       CC      TTCC      AGATGGT        A
|||  |||||||||       ||      ||||      |||||||
GTG  GGAGATTTG       GG      AAGG      TCTATCA        /
   A-          CGCTCA  TATGT    ATTTT        AAGTGAT
```

Fig. 142D/1

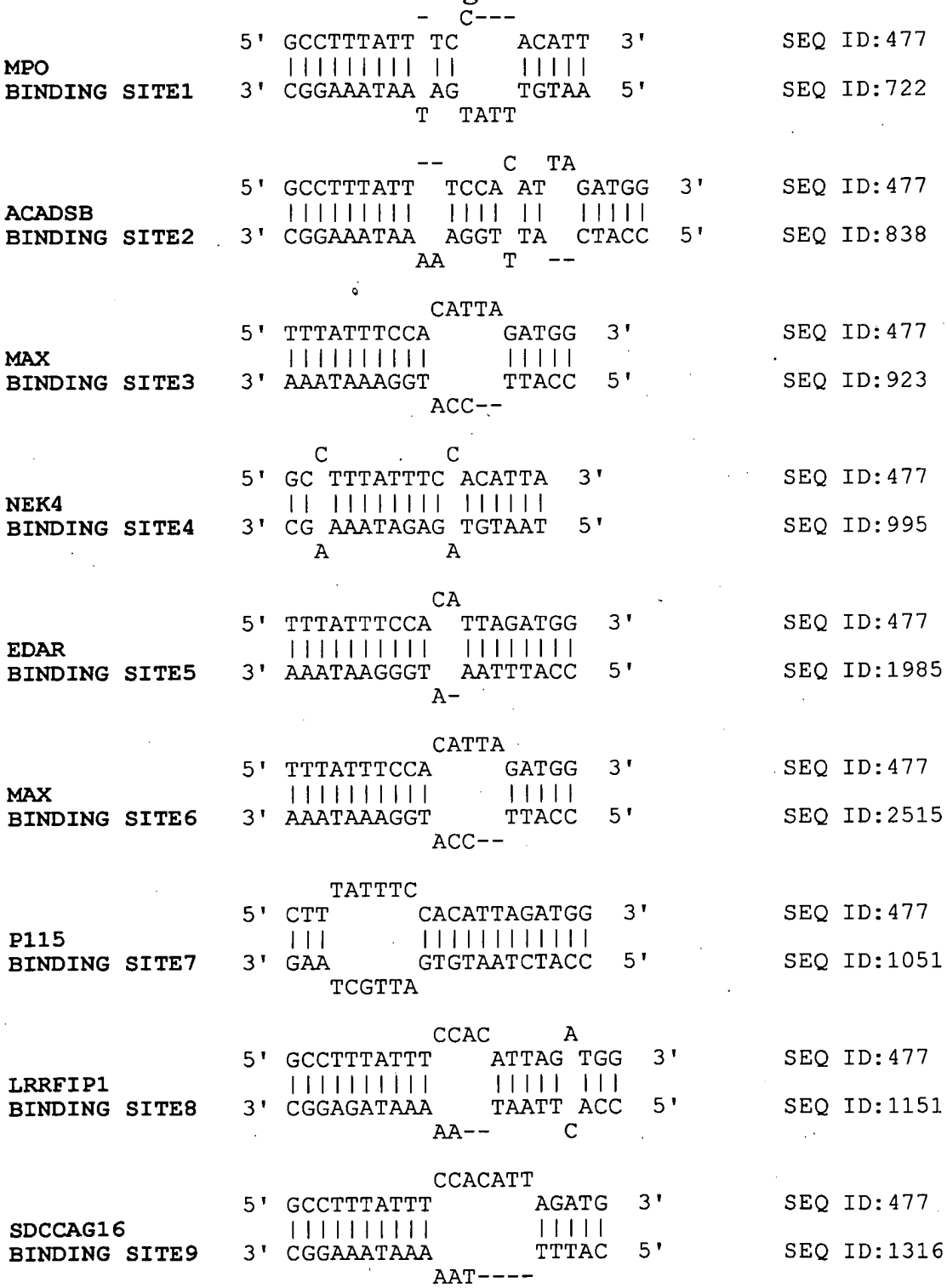

- C---
5' GCCTTTATT TC ACATT 3' SEQ ID:477
MPO
BINDING SITE1 3' CGGAAATAA AG TGTAA 5' SEQ ID:722
T TATT
-- C TA
5' GCCTTTATT TCCA AT GATGG 3' SEQ ID:477
ACADSB
BINDING SITE2 3' CGGAAATAA AGGT TA CTACC 5' SEQ ID:838
AA T --
CATTA
5' TTTATTTCCA GATGG 3' SEQ ID:477
MAX
BINDING SITE3 3' AAATAAAGGT TTACC 5' SEQ ID:923
ACC--
C C
5' GC TTTATTTC ACATTA 3' SEQ ID:477
NEK4
BINDING SITE4 3' CG AAATAGAG TGTAAT 5' SEQ ID:995
A A
CA
5' TTTATTTCCA TTAGATGG 3' SEQ ID:477
EDAR
BINDING SITE5 3' AAATAAGGGT AATTTACC 5' SEQ ID:1985
A-
CATTA
5' TTTATTTCCA GATGG 3' SEQ ID:477
MAX
BINDING SITE6 3' AAATAAAGGT TTACC 5' SEQ ID:2515
ACC--
TATTTC
5' CTT CACATTAGATGG 3' SEQ ID:477
P115
BINDING SITE7 3' GAA GTGTAATCTACC 5' SEQ ID:1051
TCGTTA
CCAC A
5' GCCTTTATTT ATTAG TGG 3' SEQ ID:477
LRRFIP1
BINDING SITE8 3' CGGAGATAAA TAATT ACC 5' SEQ ID:1151
AA-- C
CCACATT
5' GCCTTTATTT AGATG 3' SEQ ID:477
SDCCAG16
BINDING SITE9 3' CGGAAATAAA TTTAC 5' SEQ ID:1316
AAT----

FIG. 145A

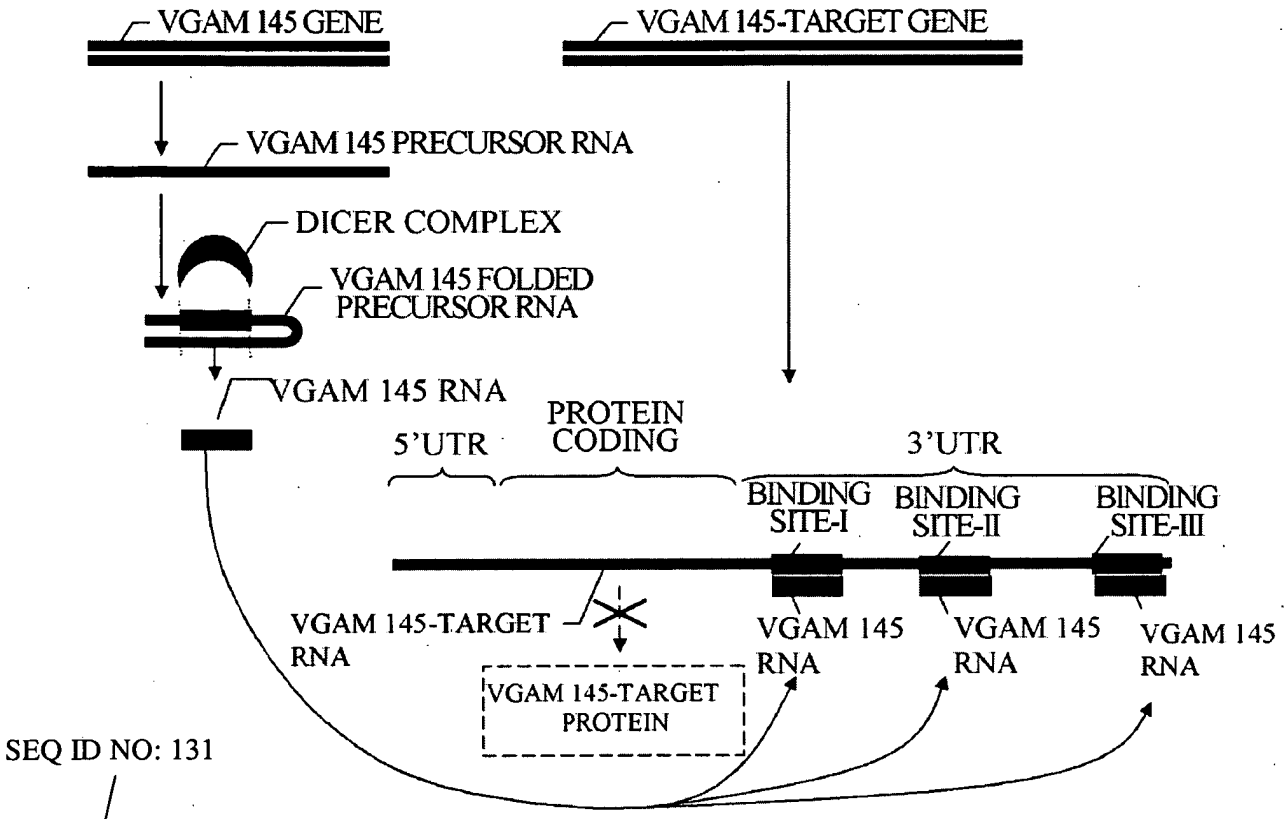


FIG. 145B

GGCTATTCTGGCGGCTAGAATGGCATAATCCGGATGTTG TGTAGTACAAGTGGCTGCTATTTCGGCTGCCAGAGTGTC C **SEQ ID:40001**

TGCTATTTCGGCTGCCAGAGTGTC **SEQ ID:40002**

SEQ ID NO: 480

FIG. 145C

```
  C            TA        TAAT   GA   TGT
GG TATTCTGGCGGC  GAATGGCA    CCG  TGT   G
|| ||||||||||||  ||||||||    |||  |||
CC GTGAGACCGTCG  TTTATCGT    GGT  ACA   T
  T           GC        C---   GA   TGA
```

Fig. 145D/1

```
                    A    GGCTGC
                5' TGCT TTTC      CAGAGTGT  3'        SEQ ID:480
TBXAS1             |||| ||||      ||||||||
BINDING SITE1   3' ACGA AAAG      GTCTCACA  5'        SEQ ID:798
                    G    A-----

                         C  C  CCAG
                5' TGCTATTT GG TG    AGT  3'          SEQ ID:480
INHBA              |||||||| || ||    |||
BINDING SITE2   3' ACGATAAA CC AC    TCA  5'          SEQ ID:904
                         C  A  AAGA

                    A    GGCTGC
                5' TGCT TTTC      CAGAGTGT  3'        SEQ ID:480
TBXAS1             |||| ||||      ||||||||
BINDING SITE3   3' ACGA AAAG      GTCTCACA  5'        SEQ ID:2182
                    G    A-----

                         C      CA---
                5' TGCTATTT GGCTGC     GAGTGT  3'     SEQ ID:480
KIAA1056           |||||||| ||||||     ||||||
BINDING SITE4   3' ACGATAAA CCGACG     TTCACA  5'     SEQ ID:1576
                         -      CCGAC

                      G  GCC
                5' TTTCG CT   AGAGTGTC  3'           SEQ ID:480
LOC91752           ||||| ||   ||||||||
BINDING SITE5   3' AAAGT GA   TCTCACAG  5'           SEQ ID:2779
                       A  ---

                    A        --     A
                5' TGCT TTTCGGCT  GCCAG GTGTC  3'    SEQ ID:480
LOC197342          |||| ||||||||  ||||| |||||
BINDING SITE6   3' ACGA AAGGCCGA  CGGTC CACAG  5'    SEQ ID:3424
                    C        GT     -
```

FIG. 147A

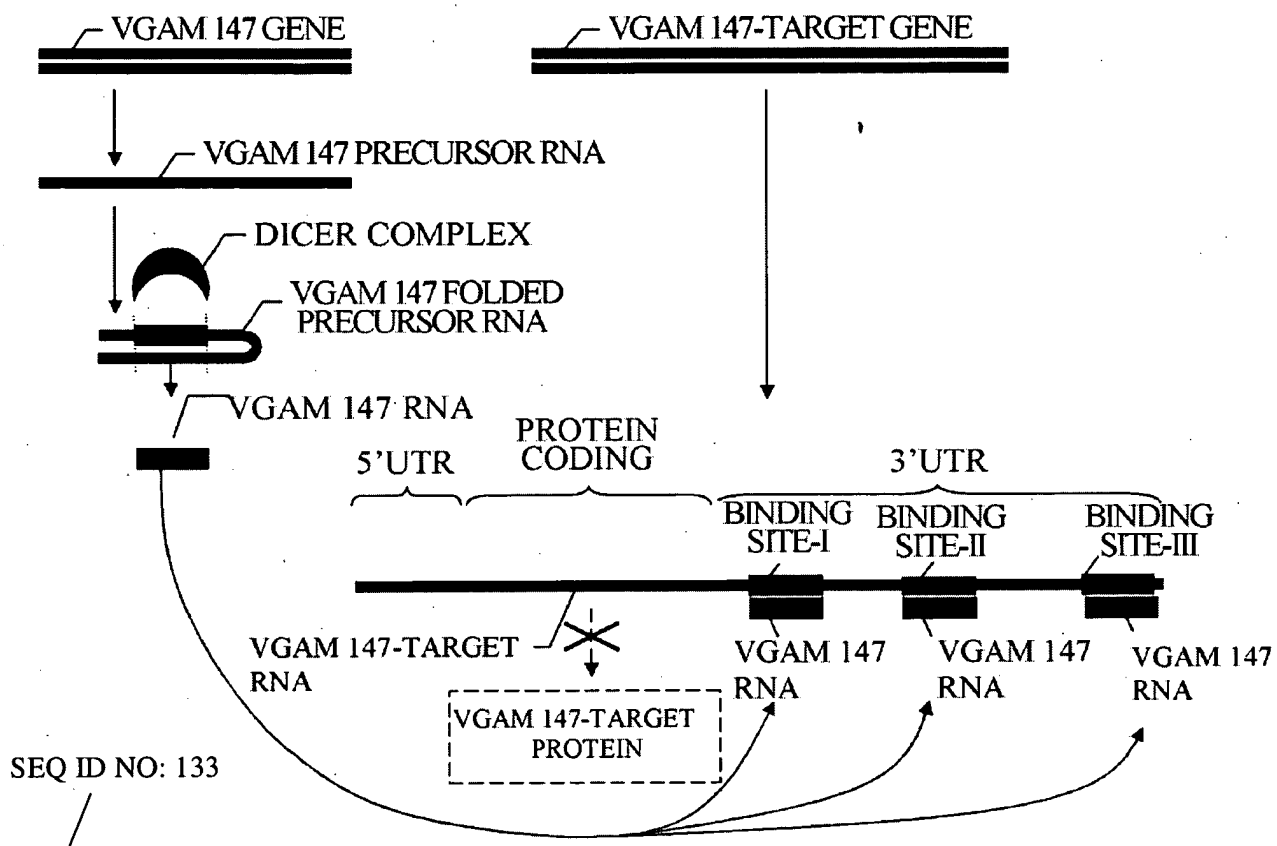


FIG. 147B

TCTGGTTCTATGTTCCTCGTTTCCTGTATTCTTTTTAAGAT **SEQ ID:40001**
CGAGGAACGCCATAATATCAGA

TCTATGTTCCTCGTTTCCTGTATT **SEQ ID:40002**

SEQ ID NO: 482

FIG. 147C

```
      TC   ---         TT  C  TATT
TCTGGT  TAT   GTTCCTCG  TC TG    C
||||||  |||   ||||||||  || ||
AGACTA  ATA   CAAGGAGC  AG AT    /
      TA   CCG        T-  A  TTTT
```

Fig. 147D/1

```
                    T    --
                5' GT CCTC  GTTTCCTGTATT  3'          SEQ ID:482
ATP10C             || ||||  ||||||||||||
BINDING SITE1   3' CA GGAG  CAAAGGACATAA  5'          SEQ ID:2062
                     T    AA

                       C  C-
                5' TGTT CT  GTTTCCTGT  3'            SEQ ID:482
CASP10             |||| ||  |||||||||
BINDING SITE2   3' ACAA GA  CAAGGGACA  5'            SEQ ID:2304
                       A  AA

                          C  C
                5' TCTATGTT CT GTTTCC  3'            SEQ ID:482
ZNF36              |||||||| || ||||||
BINDING SITE3   3' AGATACAA GA CAAAGG  5'            SEQ ID:3627
                          A  -

                          CCTCG
                5' TCTATGTT     TTTCCTGT  3'         SEQ ID:482
P37NB              ||||||||     ||||||||
BINDING SITE4   3' AGATACAA     AAAGGGTA  5'         SEQ ID:1254
                          AAA--

                          CC  GTTTC
                5' TCTATGTT  TC     CTGTAT  3'       SEQ ID:482
RAP140             ||||||||  ||     ||||||
BINDING SITE5   3' AGATACAA  AG     GACATA  5'       SEQ ID:1613
                          -- ATA--

                        CC  -
                5' TATGTT  TC GTTTCCTGTATT  3'       SEQ ID:482
DORFIN             ||||||  || ||||||||||||
BINDING SITE6   3' GTACAA  AG TAAAGGACATAA  5'       SEQ ID:1630
                         AT  A

                     TA    CC   TT
                5' TC  TGTT  TCG  TCCTGTATT  3'      SEQ ID:482
FLJ21313           ||  ||||  |||  |||||||||
BINDING SITE7   3' AG  ACAA  AGT  AGGACATAA  5'      SEQ ID:2037
                     TC    AA   --

                       AT    CTC
                5' TCT  GTTC   GTTTCCTGTATT  3'      SEQ ID:482
KIAA1819           |||  ||||   ||||||||||||
BINDING SITE8   3' AGA  CAAG   TAGAGGACATAA  5'      SEQ ID:2865
                       C-    A--

                          C  C    CC
                5' TCTATGTT CT GTTT  TGTATT  3'      SEQ ID:482
LOC127002          |||||||| || ||||  ||||||
BINDING SITE9   3' AGATACAA GA CAAA  ATATAA  5'      SEQ ID:3002
                          A  -    A-
```